DESCRIPTION OF THE PROPOSED EXPERIMENT IN NON TECHNICAL LANGUAGE

Cystic fibrosis (CF) is a serious genetic disease characterized by obstruction of the airways with thick mucous and frequent infections which destroy lung tissue. The disease is fatal with an average life expectancy of approximately *30* years [1]. The gene which is abnormal in CF is normally responsible for producing a protein called the cystic fibrosis transmembrane conductance regulator, or CFTR. This protein controls the salt balance in the airways of the lungs; when the protein is not normal, excessive thick mucous is produced resulting in the complications described above. Treatment, which includes antibiotics, good nutrition and mucous clearance, has improved; however, no treatment corrects the basic underlying defect, and the lung problems invariably worsen with time.

Because cystic fibrosis is a genetic disease, adding a normal CFTR gene to cells that line the affected airways could restore normal function to these cells and thereby correct the problems associated with the disease. This approach is called gene therapy. In laboratory studies we have successfully inserted a normal CFTR gene into airway cells of animals and cells grown in culture. A lipid (a fat-like molecule) was used to carry the CFTR gene into these cells. Studies in laboratory animals have shown that the lipid:DNA mixture does not cause serious damage to the lung at low to medium doses, although at high doses it can cause a more severe inflammatory response.

The proposed protocol is designed to test 1) whether cationic lipids can be used to safely transfer the normal CFTR gene into the airway cells of CF patients and 2) whether transfer of the normal CFTR gene will allow the affected airway cells to function normally.

The cells lining the inside of the nose are very similar to those which line the airways in the lung. Therefore this protocol will be performed in the nose, since it is easily accessible, presents a lower risk, and the specific outcome can be easily evaluated. In order to minimize the risk to CF patients and to test the safety of applying the lipid alone, normal volunteers will be studied in the first part of the protocol. Small drops of the lipid in water will be applied to the inside of the nose every ten minutes until the correct dose has been given. Three different doses of lipid alone will be tested, and the highest of the three doses determined to be safe in normal volunteers will be mixed with the DNA containing the CFTR gene and applied to the nose of CF patients. Safety of the applications in both the normal volunteers and the CF patients will be assessed during the study by both clinical exam and routine laboratory tests. Transfer of the CFTR gene into the cells lining the nose of CF patients will be tested in two ways. In healthy individuals a small electrical charge or voltage can be measured in the cells lining the nose; this voltage is abnormal in CF patients. The voltage in the nose of CF patients will be measured before and after gene delivery. Return of this voltage towards normal levels will signal that the CFTR gene has been delivered successfully. Second, a brush will be used to collect treated cells lining the nose of CF patients after gene delivery. These cells will be tested for the presence of the normal CFTR gene to confirm successful gene transfer.

Completion of this protocol will determine whether lipid can be safely used to mediate gene transfer in CF patients. The data obtained from this initial protocol will be used to devise new protocols for the safe and effective delivery of the normal CFTR gene to airway cells of CF patients.

1. *Cystic fibrosis foundation patient registry annual data report,* 7993. September, 1994, Cystic Fibrosis Foundation